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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/996,838	11/29/2001	Hans Hofland	P 23,643-A USA	6395

7590 05/28/2008

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EXAMINER	
EPPS FORD, JANET L	
ART UNIT	**PAPER NUMBER**
1633	

MAIL DATE	DELIVERY MODE
05/28/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/996,838	HOFLAND ET AL.	
	Examiner	Art Unit	
	Janet L. Epps-Ford	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 February 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1, 7, 14-15, and 33-38* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,7,14,15 and 33-38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1, 7, 14-15 and new claims 33-38.

Response to Arguments

Claim Rejections - 35 USC § 112

2. The rejection of claims 1, 7, 11, and 14-15 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, in response to Applicant's amendment.

3. Although it was stated in the prior Office Action that the instant claims would be allowable once Applicant's have amended the claims to overcome the prior rejection under 112, 2nd ¶, upon a closer examination of the prior art of record in order to confirm the allowability of the pending claims, and in view of an updated search, the following rejection was considered necessary since there is no record of unexpected properties associated with the stable colloids formed by the process recited in the instant claims.

Claim Rejections - 35 USC § 103

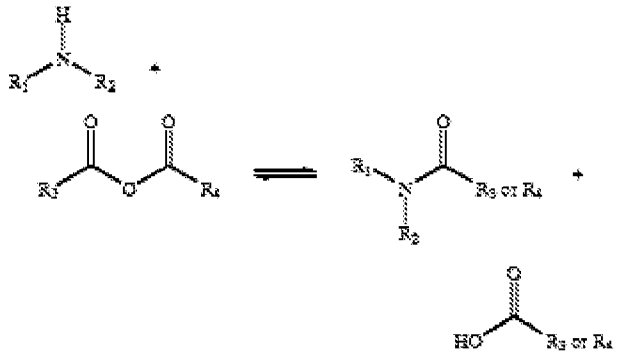
4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Claims 1, 7, 14-15, and 33-38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Monahan et al. (6,630,351) and Monahan et al. (6,379,966), in view of Semple (US Patent No. 6,287,591 B1) taken with Trubetskoy (US 2003/0026841 A1).

Monahan et al. describe the process for surface recharging of a colloid system. Specifically Monahan et al. taught: "[I]t can be concluded that addition of low charge density polyanion to the cationic DNA/PLL particles results in particle surface charge reversal while maintaining condensed DNA core intact," (see col. 9-10).

In a preferred embodiment Monahan et al. teach the production of surface modified cationic polymers complexes modified with a pH-Labile Bond, wherein, for example, the cationic head groups of the polymer is reacted with an anhydride containing compound, see for example col. 38:



Reaction of an amine and an anhydride to form an amide acid.

Modified polymers with labile bonds have the following generalized structure: A-B-A where A is a monomer and B is a pH-labile linkage, A-B-C where A is a monomer, B is a pH-Labile linkage and C is an interaction modifier. The labile group may be added to the polymer during polymer synthesis or the labile group may be added to the polymer after polymerization has occurred (see col. 39). Moreover, "[I]f the functional group A is an amine the B can include, but is not limited to, an isothiocyanate, isocyanate, acyl azide, ***N-hydroxysuccinimide***, sulfonyl chloride, aldehyde (including

formaldehyde and glutaraldehyde), ketone, epoxide, carbonate, imidoester, carboxylate activated with a carbodiimide, alkylphosphate, arylhalides (difluoro-dinitrobenzene), ***anhydride***, or acid halide, p-nitrophenyl ester, o-nitrophenyl ester, pentachlorophenyl ester, pentafluorophenyl ester, carbonyl imidazole, carbonyl pyridinium, or carbonyl dimethylaminopyridinium. In other terms when function A is an amine then function B can be acylating or alkylating agent or amination agent." (see col. 41).

Preferred cationic polymers of Monahan et al. include: polylysine, polyarginine (*which comprises guanidinium groups)*, polyornithine, DEAE dextran, polybrene, and polyethylenimine, which are described as potential effective intracellular delivery agents, see col. 6, lines 1-8.

See also col. 74, example 7 wherein a preformed complex of DNA and polylysine is reacted with a derivative of maleic anhydride. It is noted that citraconic anhydride is a derivative of maleic anhydride, see col. 39, wherein R2 is methyl.

However, Monahan et al. (6,630,351) does not exemplify a process wherein N-hydroxysuccinimide or citraconic anhydride in a method for recharging a DNA/cationic polymer complex.

Monahan et al. (6,379,966), also discloses a process for the formation of a stable colloid, wherein said process comprises that the addition of citraconic anhydride to the cationic polymer poly-L-lysine, and the formation of citraconylpoly-L-lysine, and the addition of this compound to a complex of DNA and poly-L-lysine, wherein the overall zeta potential of the formed particles of this reaction is negative (see col. 25, lines 27-65). Additionally, Monahan et al. teach the use of NHS ester to react with cationic

polymers to form anionic polymers. Additionally, it is clear that the invention of Monahan et al. is specifically designed for modifying DNA-polymer complexes to comprise a negative zeta potential for the express purpose of delivering nucleic acid in cells (see abstract).

Semple et al. (see col. 9) teach the following (as set forth in the Office Action mailed 9/09/04, see page 8):

> The methods and composition of the invention make use of certain lipids which can be present in both a charged and an uncharged form. For example, amino lipids which are charged at a pH below the pK_a of the amino group and substantially neutral at a pH above the pk_a can be used in a two-step process. First, lipid vesicles can be formed at the lower pH with (cationic) amino lipids and other vesicle components in the presence of nucleic acids. In this manner the vesicles will encapsulate and entrap the nucleic acids. Second, the surface charge of the newly formed vesicles can be neutralized by increasing the pH of the medium to a level above the pK_a of the amino lipids present, i.e., to physiological pH or higher. Particularly advantageous aspects of this process include both the facile removal of any surface adsorbed nucleic acid and a resultant nucleic acid delivery vehicle which has a neutral surface. Liposomes or lipid particles having a neutral surface are expected to avoid rapid clearance from circulation and to avoid certain toxicities which are associated with cationic liposome preparations.

The teachings of Semple et al. clearly suggests modifying the surface of DNA/cationic polymer particles containing formulation, the particles would resist degradation from *in vivo* circulation and not produce certain toxicities, which are associated with cationic liposome preparations. Along this same rationale, Trubetskoy et al. (see page 5, paragraph 52) and Monahan et al. (6,379,966; col. 23) provide motivation for a recharging process as applied to reducing the cationic charge on liposomal vessels, to thereby enhance the efficiency of gene transfer *in vivo.* Moreover, the very reagents that Applicants use for "recharging" the cationic charge on the recited cationic polymers or polymers present in said complex are disclosed in Monahan et al. (CCA and NHS ester), for use in the same

purpose, namely for the treatment of cationic polymers to confer a negative charge in the design of a stable DNA-polymer complex for delivery into a cell. Furthermore, Trubetskoy et al. teaches that an addition of polyanionic molecules to a polymer/DNA complex would enhance the transfer activity of a DNA/cationic polymer complex.

Therefore, it would have been obvious to the ordinary skilled artisan to modify the teachings of Monahan et al. (both references) in view of Semple et al. and Trubetskoy et al. One of ordinary skill in the art would have been motivated to make this modification since as stated above it was well known in the art at the time of the instant invention, that DNA/cationic polymer complexes can be recharged to reduce the cationic surface charge and thereby enhance the transfection efficiency of the complex. Moreover, Monahan et al. (both references) suggest the use of citraconic anhydride and N-hydroxysuccinimide to modify DNA/cationic polymer complexes. Furthermore, since the prior art teaches the modification of DNA complexed with linear polyamines, and further provides motivation for the modification with NHS and CCA, absent evidence to the contrary since the general conditions of the claimed invention are disclosed in the prior art the ordinary skilled artisan would also expect that complexes formed by the prior art teachings would also possess the same properties. Therefore, if the amine groups within the DNA/linear polyamine complexes (as described in the instant claims) are accessible for reaction with NHS and CCA, one of ordinary skill in the art (absent evidence to the contrary) would also expect that those complexes formed as per the cited references would also possess the same properties.

6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L. Epps-Ford whose telephone number is 571-272-0757. The examiner can normally be reached on M-F, 10:00 AM through 6:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Janet L. Epps-Ford/
Primary Examiner, Art Unit 1633

JLE